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published in
Value in Health
2020

DOI (link to publisher)
10.1016/j.jval.2019.12.009

document version
Publisher's PDF, also known as Version of record

ScienceDirect

Contents lists available at sciencedirect.com
Journal homepage: www.elsevier.com/locate/jval

Economic Evaluation

Cost-Effectiveness of Radiofrequency Denervation for Patients With Chronic Low Back Pain: The MINT Randomized Clinical Trials

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ABSTRACT

Objectives: To evaluate the cost-effectiveness of radiofrequency denervation when added to a standardized exercise program for patients with chronic low back pain.

Methods: An economic evaluation was conducted alongside 3 pragmatic multicenter, nonblinded randomized clinical trials (RCTs) in The Netherlands with a follow up of 52 weeks. Eligible participants were included between January 1, 2013, and October 24, 2014, and had chronic low back pain; a positive diagnostic block at the facet joints (n = 251), sacroiliac (SI) joints (n = 228), or a combination of facet joints, SI joints, and intervertebral discs (n = 202); and were unresponsive to initial conservative care. Quality-adjusted life-years (QALYs) and societal costs were measured using self-reported questionnaires. Missing data were imputed using multiple imputation. Bootstrapping was used to estimate statistical uncertainty.

Results: After 52 weeks, no difference in costs between groups was found in the facet joint or combination RCT. The total costs were significantly higher for the intervention group in the SI joint RCT. The maximum probability of radiofrequency denervation being cost-effective when added to a standardized exercise program ranged from 0.10 in the facet joint RCT to 0.17 in the SI joint RCT irrespective of the ceiling ratio, and 0.65 at a ceiling ratio of €30 000 per QALY in the combination RCT.

Conclusions: Although equivocal among patients with symptoms in a combination of the facet joints, SI joints, and intervertebral discs, evidence suggests that radiofrequency denervation combined with a standardized exercise program cannot be considered cost-effective from a societal perspective for patients with chronic low back pain originating from either facet or SI joints in a Dutch healthcare setting.

Keywords: economic evaluation, low back pain, radiofrequency denervation, randomized controlled trials.

VALUE HEALTH. 2020; 23(5):585–594

Introduction

Low back pain is a global public health problem and has major social and economic consequences.[1–3] Low back pain is the leading worldwide cause of years lost to disability, and its burden is growing because of the aging population.[4] Low back pain was responsible for 60.1 million years lived with disability in 2015, an increase of 54% since 1990.[4] Disability from low back pain is highest in working age groups,[4] and its economic impact is comparable to that of other prevalent, high-cost conditions, such as cardiovascular diseases and cancer.[5]

The cost of low back pain in The Netherlands was estimated to be €3.5 billion in 2007, of which the majority of costs were due to productivity losses and were attributable to patients with chronic symptoms.[6,7] A systematic review concluded that 33% of patients recovered from low back pain symptoms within 3 months, but 65% of patients still reported pain 1 year after onset.[8]

Suggested sources of low back pain are the facet joints, the sacroiliac (SI) joints, and the intervertebral discs; these are all classified as mechanical low back pain.[9] Radiofrequency denervation is a common treatment for patients with chronic mechanical low back pain. This treatment aims to prevent the

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https://doi.org/10.1016/j.jval.2019.12.009

conduction of pain sensation by damaging the pain-conducting nerve using local heat released from an electric current.[10] The effectiveness of radiofrequency denervation has not been demonstrated unequivocally, and its cost-effectiveness is unknown.[11–13] The costs of radiofrequency denervation, as estimated by the Dutch Healthcare Council, are between €6 million to €10 million per year for a population of 17 million.[14]

In 2012, the Ministry of Health, Welfare, and Sport in The Netherlands funded a project to evaluate the effectiveness and cost-effectiveness of radiofrequency denervation for patients with chronic low back pain. This project was embedded in a new funding model by the Dutch government and the Netherlands Organization for Health Research and Development (voorwaardelijke financiering [in Dutch]), in which all relevant stakeholders (the National Health Care Institute, health insurance companies, the Netherlands Organization for Health Research and Development, the Dutch Society for Anesthesiology, and a patient representative) were closely involved.[15] The current project was the first in this funding model and was aimed at informing the Dutch government about a pending decision to include radiofrequency denervation for patients with chronic low back pain in the Dutch basic health insurance package.[15] Based on a multidisciplinary guide to mechanical low back pain, developed by the Dutch Societies of Anesthesiology, Neurosurgery, and Orthopedic surgery,[16] the opportunity was given to continue reimbursement for radiofrequency denervation for a period of 4 years. This study was intended to provide a definitive answer on the inclusion of radiofrequency denervation in the Dutch basic health insurance package.

The results on the clinical effectiveness of radiofrequency denervation were recently published[17] and did not support radiofrequency denervation as an add-on to a standardized exercise program. Based on these results, we also recommend that future studies with a focus on patient selection, treatment techniques, and outcome parameters should be performed. Debate exists as to whether trial-based economic evaluations should still be performed if positive clinical effects are lacking. Nevertheless, as a lack of statistical differences between therapies does not necessarily mean that they are identical, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Cost-Effectiveness Analysis Randomized Clinical Trial (CEA-RCT) taskforce recommends researchers perform a CEA if clinical results are negative.[18] Therefore the aim of this study was to evaluate the cost-effectiveness of adding radiofrequency denervation to a standardized exercise program compared with maintaining a standardized exercise program alone for patients with chronic mechanical low back pain from a societal perspective.

This study serves as an example of a successful new funding model, which can increase the implementation of cost-effectiveness study results into clinical guidelines.

Methods

Study Design

An economic evaluation was conducted alongside 3 RCTs to evaluate the effectiveness of minimal interventional treatments for patients with chronic low back pain. This was called the MINT study.[17] Information about the study protocol and clinical effectiveness is published elsewhere.[17,19]

All the trials were registered in the Dutch Trial Register (NTR3531). Patients were included in 16 multidisciplinary pain clinics in The Netherlands. Local research governance was obtained from these clinics, and the Medical Ethics Committee of the Erasmus University Medical Centre in Rotterdam (MEC 2012-079) granted ethical approval. All participants gave written informed consent.

Procedure

Prior to the start of the study, 50 pain specialists from within the Dutch Society for Anesthesiology reached consensus about the study population, diagnostic procedures, and interventions for this study. There was consensus that the procedures and study methods reflected best practice in The Netherlands. These methods follow the evidence-based interventional pain medicine according to clinical diagnoses guidelines of Van Zundert et al.[9]

Patient Population

The Dutch Society of Anesthesiologists selected 16 multidisciplinary pain clinics to participate in the study. In the participating clinics, pain specialists screened consecutive patients with chronic low back pain. Chronic low back pain was defined as having had symptoms for more than 3 months and having indicated these long-lasting symptoms to the physician treating the pain.

nclusion criteria:

- Patients aged between 18 and 70 years.
- No improvement in symptoms after conservative care.
- Pain related to the facet joint; the SI joint; or a combination of the facet joint, SI joint, and/or intervertebral disc. The source of pain was determined by a patient's medical history and a clinical examination that followed a standard format and was performed by an experienced clinician. Reported history and the clinical examination were followed by a diagnostic block. A full description of the diagnostic block procedures can be found in Appendix A in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.12.009.

Exclusion criteria:

- Pregnancy
- Severe psychological problems (determined with psychological questionnaires)
- Involvement in work-related conflicts or claims
- A body mass index (BMI) $>$ 35
- Anticoagulant drug therapy or coagulopathy

More details on the study design, participating clinics, and participants can be found elsewhere.[17,19]

Randomization and Masking

Randomization was performed at the individual level, stratified per pain clinic, and done in blocks of 4. Participants were allocated (1:1) to receive either radiofrequency denervation in combination with a standardized exercise program (intervention group) or a standardized exercise program alone (control group).

Neither caregivers nor participants were blinded; however, data interpretation of results was blinded to treatment allocation. Participants' expectations before and satisfaction after treatment were measured to objectify a possible risk of bias (ie, lack of blinding of patients tends to exaggerate the effect sizes)[20] owing to the nonblinded study design.[21,22]

Intervention and Comparator Group

All participants completed an 8- to 12 hour-long exercise program within 3 months of enrollment in 1 of 102 participating physical therapy practices. The program was based on Dutch

physical therapy guidelines and focused on quality of movement and behavior.[23] Psychological care was provided if needed.

Participants in the intervention group also received radiofrequency denervation within 1 week after the first exercise session. The details of the radiofrequency denervation technique can be found in Appendix A in Supplemental Materials (found at https://doi.org/10.1016/j.jval.2019.12.009).

Participants were asked to refrain from the use of co-interventions during the 3-month intervention period. Analgesics were not prescribed to discourage the use of these medications, but over-the-counter medication was not restricted. After the 3-month intervention period, participants were allowed to receive additional treatments, including radiofrequency denervation, if deemed necessary.

Health-Related Quality of Life

At baseline and 3, 6, 9, and 12 months after start of the intervention, the patients' health states were assessed using the EuroQol 5D Health Questionnaire 3-level version (EQ-5D-3L). Using the Dutch EQ-5D-3L tariff,[8,24] these health states were converted into utility values (0 = dead; 1 = full health).[17,25] Quality-adjusted life-years (QALYs) were calculated using the area under the curve approach.

Costs

In line with Dutch guidelines, costs were assessed from a societal perspective, meaning that all costs were included irrespective of who paid or benefited.[26] Intervention costs were estimated using the accounting records of 2 of the 16 participating clinics; the costs of all 16 clinics were expected to be comparable. Data on other healthcare utilization, informal care, unpaid productivity, and absenteeism as a result of back pain were collected using 3 monthly, self-reported web-based cost questionnaires.[27] Healthcare utilization included primary care (eg, general practitioner care, physiotherapy, manual therapy, chiropractic care, and exercise therapy), secondary care (eg, hospitalization and diagnostic and therapeutic interventions), and the use of prescribed and over-the-counter medication. Healthcare utilization was valued using Dutch standard costs and prices of professional organizations if standard costs were not available.[26] Medication use was valued using unit prices of the Royal Dutch Society of Pharmacy.[28] Informal care included care by family, friends, and other volunteers and was valued according to the proxy good method using an estimate of the hourly cost of a housekeeper.[26] Absenteeism was measured with the Productivity and Disease Questionnaire (PRODISQ).[29] In accordance with the friction cost approach (friction period = 23 weeks), absenteeism was valued using age- and sex-specific price weights.[26] Unpaid productivity costs included all hours of volunteer work and domestic and educational activities that participants were not able to perform owing to their chronic low back pain; these were valued using the aforementioned proxy good method as well.[26] All costs were converted to 2014 euros using consumer price indices.[30] Discounting of costs and effects was not necessary because the follow-up of the trial was 1 year.[31] Appendix B in Supplemental Materials (found at https://doi.org/10.1016/j.jval.2019.12.009) lists the main cost categories and prices used in this economic evaluation.

All web-based cost questionnaires were sent at baseline and 3, 6, 9, and 12 months after start of treatment.

Statistical Analyses

Cost-utility analyses (CUA) were performed by intention-to-treat. Baseline characteristics were compared between intervention- and control-group participants.[32,33] Missing data for the economic evaluation were handled using a multiple imputation by chained equations approach.[34] The imputation model included sex, smoking, marital status, age, BMI, back pain complaint history, education, treatment expectations, and relevant baseline effect measure values. Ten complete data sets were created so that the loss of efficiency would be smaller than 5%. Pooled estimates were calculated according to Rubin's rules.[32] Mean between-group cost differences were calculated for total and disaggregated costs. Seemingly unrelated regression (SUR) analyses were performed in which effect and cost differences were adjusted for the same baseline characteristics as in the imputation model, taking into account the possible correlation between cost and effect differences.[35] Incremental cost-effectiveness ratios (ICERs) were calculated by dividing the difference in total adjusted costs by the difference in adjusted QALYs. Uncertainty surrounding the cost differences and ICERs were estimated using bias corrected and accelerated (BCA) bootstrapping techniques (5000 replications) and graphically presented in cost-effectiveness planes.[36] Cost-effectiveness acceptability curves were estimated to indicate the probability of radiofrequency denervation being cost-effective when added to a standardized exercise program compared with the same standardized exercise program alone at different values of willingness to pay (further referred to as the ceiling ratio).[37] In these analyses, SUR analyses and BCA bootstrapping were nested in multiple imputation, meaning that multiple imputation was used to generate 10 complete data sets, after which the SUR and BCA bootstrapping methods were applied to each of the complete data sets. Then the intermediate results per completed data set were pooled using Rubin's rules.[38]

Predetermined sensitivity analyses (SA) were performed to assess the robustness of the results by comparing the SF-6D and EQ-5D-3L (SA1) and comparing the friction cost approach to the human capital approach (SA2). Furthermore, a complete-case analysis (SA3) and a sensitivity analysis using only short-term (3-month) outcomes was performed (SA4).

The economic evaluations were performed using STATA (V12, Stata Corp, College Station, TX).

Results

Study Participants

Eligible participants were included between January 1, 2013 and October 24, 2014 and followed up for 52 weeks.

In total, 251 patients were included in the facet joint trial (125 intervention group participants and 126 control group participants), 228 patients in the SI joint trial (116 intervention group participants and 112 control group participants), and 202 in the combination group trial (103 intervention group participants and 99 control group participants).

Baseline characteristics were similar between the groups (Table 1), except for the time since the first episode of low back pain, which was longer in the intervention group compared with the control group in all 3 RCTs.

Complete data on all measurements during the 52-week follow-up was obtained from 179 participants (73%) in the facet joint RCT, 175 participants (77%) in the SI joint RCT, and 89 (44%) participants in the combination trial. Variables with significant differences between participants with complete and incomplete data in both treatment groups were included in the imputation model (see Appendix C in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.12.009).

Table 1. Baseline characteristics.

Characteristics	Facet RCT		SI joint RCT		Combination group RCT	
	Intervention, n = 125*	Control, n = 126*	Intervention, n = 116*	Control, n = 112*	Intervention, n = 103*	Control, n = 99*
Age in years (SD)	52.9 (11.5)	52.6 (10.8)	51.58 (10.94)	51.13 (12.22)	50.80 (11.33)	53.31 (10.35)
Female (no. [%])	65 (55.6)	60 (51.7)	87 (75.0)	79 (76.0)	64 (65.3)	66 (74.2)
BMI (SD)	26.7 (5.2)	27.6 (4.3)	26.73 (4.17)	26.76 (4.53)	26.84 (3.82)	26.43 (4.25)
Smoker (no. [%])	34 (29.1)	34 (29.3)	29 (26.6)	31 (29.8)	23 (23.5)	26 (29.2)
Education†						
Low (no. [%])	57 (48.7)	64 (55.2)	59 (54.1)	53 (51.5)	52 (53.6)	43 (48.3)
Moderate (no. [%])	35 (29.9)	34 (29.3)	32 (29.4)	32 (31.1)	33 (34.0)	32 (36.0)
High (no. [%])	21 (17.9)	16 (13.8)	18 (16.5)	18 (17.5)	12 (12.4)	14 (15.7)
History of back pain complaints						
Time since first experience with low back pain in months (median [IQR])	146 (50-267)	100 (37-186)	97.33 (37.51-228.12)	65.08 (27.08-144.21)	120.58 (37.32-222.04)	97.33 (32.33-192.58)
Time since current episode with low back pain in months (median [IQR])	31 (12-103)	27 (11-73)	30.33 (12.17-76.03)	24.33 (12.17-66.58)	36.50 (12.17-121.67)	32.33 (8.00-97.19)
Married/living with a partner (no. [%])	93 (74.4)	98 (77.8)	85 (78.0)	82 (79.6)	66 (67.3)	68 (76.4)
Expectations (CEQ)						
Credibility (0-27)	21.4 (3.9)	19.5 (5.5)	21.36 (4.51)	19.88 (5.31)	20.10 (4.70)	17.07 (5.99)
Expectancy (0-27)	18.9 (4.6)	17.4 (5.2)	18.75 (4.99)	18.23 (5.31)	16.88 (5.78)	14.38 (6.24)
Having a paid job	64 (51.2)	66 (58.9)	66 (61.1)	50 (44.6)	48 (55.8)	44 (55.7)
Origin of back pain (no.)						
Facet & SI joint					69	70
Facet & disc					18	18
SI joint & disc					6	1
Facet & SI joint & disc					3	6
Unknown					7	4
Outcomes						
Mean (SD) Quality of life (EQ-5D)	0.5 (0.3)	0.5 (0.3)	0.50 (0.27)	0.56 (0.27)	0.49 (0.28)	0.52 (0.28)

BMI indicates body mass index; CEQ, credibility expectancy questionnaire; EQ-5D, EuroQol-5D; IQR, interquartile range; NRS, numeric rating system; RCT, randomized controlled trial; SD, standard deviation; SI, sacroiliac.
*Results are presented of the 233 participants who had complete baseline data.
†Low = pre-school, primary school, lower secondary school; moderate = higher secondary school, undergraduate; high = tertiary, university, or postgraduate.

Facet Joint Trial

In the facet joint trial, the minimal interventional treatment costs were estimated at €909 per participant, and the difference in total societal costs was €1185 (95% confidence interval [CI], 78-2472). All of the between-group differences in the QALY disaggregate costs were not statistically significant (Table 2; Table 3). The ICER indicated that radiofrequency denervation combined with a standardized exercise program was dominated by a standardized exercise program alone (ie, the combination was more costly and less effective; Table 3 and Appendix D in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.12.009). The maximum probability of the intervention being cost-effective in comparison with a standardized exercise program was low (0.10) at all ceiling ratios (Fig. 1). Although slightly different results were found in the various sensitivity analyses, the overall conclusion of this study would not change when using any of these different approaches (Table 3 and Appendix E in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.12.009).

Sacroiliac Joint Trial

In the SI joint trial, minimal interventional treatment costs were estimated at €799 per participant. The primary healthcare costs of €414 (95% CI, 49-728), medication costs of €156 (95% CI, 5-300), and total societal costs of €1934 (95% CI, 280-3633) were significantly higher in the intervention group than in the control group (Table 2).

The ICER indicated that radiofrequency denervation combined with a standardized exercise program was dominated by a standardized exercise program alone (ie, the combination was more costly and less effective; Table 3 and Appendix F in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.12.009). The CEAC shows a low probability (≤0.17) of radiofrequency denervation being cost-effective when added to a standardized exercise program compared with a standardized exercise program alone at all ceiling ratios (Fig. 2).

The sensitivity analyses showed small differences among the complete case analysis, the short-term analysis, and the main

Table 2. Mean costs in euros per participant in the intervention and control group, and mean cost differences between both groups during the 12-month follow-up period from a societal perspective.

Cost category	Intervention group n = 125, mean (SEM)	Control group n = 126, mean (SEM)	Mean cost difference crude (95% CI)	Mean cost difference adjusted (95% CI)
Facet joint RCT				
Intervention	909 (0)	NA	NA	NA
Primary healthcare	1513 (144)	1382 (110)	130 (−210 to 507)	90 (−269 to 503)
Secondary healthcare	776 (115)	845 (107)	−70 (−362 to 210)	−2 (−280 to 299)
Medication	111 (20)	93 (22)	18 (−41 to 75)	25 (−42 to 87)
Informal care	778 (144)	756 (182)	22 (−451 to 463)	91 (−345 to 532)
Absenteeism	548 (203)	579 (190)	−32 (−502 to 544)	−30 (−568 to 665)
Unpaid productivity	1019 (189)	1131 (202)	−111 (−649 to 431)	66 (−485 to 645)
Total	5653 (4730)	4787 (453)	867 (−359 to 2146)	1185 (−78 to 2472)
Cost category	**Intervention group n = 116, mean (SEM)**	**Control group n = 112, mean (SEM)**	**Mean cost difference crude (95% CI)**	**Mean cost difference adjusted (95% CI)**
SI joint RCT				
Intervention	799 (0)	0 (0)	NA	NA
Primary healthcare	1446 (116)	1094 (129)	352 (−6 to 676)	414 (49-728)
Secondary healthcare	701 (95)	785 (147)	−83 (−492 to 220)	−445 (−353 to 220)
Medication	351 (47)	196 (50)	155 (17-281)	156 (5-300)
Informal care	1142 (326)	797 (188)	344 (−227 to 1428)	300 (−222 to 1356)
Absenteeism	1434 (417)	940 (333)	494 (−425 to 1609)	563 (−315 to 1621)
Unpaid productivity	1243 (216)	1464 (304)	−221 (−951 to 440)	−255 (−937 to 388)
Total	7116 (667)	5276 (645)	1840 (100-3645)	1934 (280-3633)
Cost category	**Intervention group n = 103, mean (SEM)**	**Control group n = 99, mean (SEM)**	**Mean cost difference crude (95% CI)**	**Mean cost difference adjusted (95% CI)**
Combination RCT				
Intervention - Diagnostic block - Radiofrequency denervation	 277 (20) 768 (71)	 174 (24) 0 (NA)	 103 (36-160) 768 (635-908)	 121 (36-187) 773 (620-950)
Primary healthcare	2123 (385)	2903 (1102)	−780 (−4113 to 651)	−883 (−4383 to 672)
Secondary healthcare	1068 (154)	1521 (307)	−454 (−1196 to 169)	−417 (−1255 to 277)
Medication	171 (218)	218 (57)	−47 (−178 to 83)	−43 (−194 to 103)
Informal care	1026 (255)	2423 (1205)	−1397 (−4811 to 80)	−1256 (−4866 to 194)
Absenteeism	3215 (959)	2611 (950)	604 (−1875 to 3101)	670 (−1923 to 3440)
Unpaid productivity	2016 (437)	2103 (595)	−87 (−1366 to 1002)	−89 (−1455 to 1165)
Total	10 664 (1477)	11 954 (2590)	−1290 (−7852 to 3453)	−1124 (−9111 to 4001)

Note. Costs are expressed in 2014 euros.
CI indicates confidence interval; NA, not applicable; RCT, randomized controlled trial; SD, standard deviation; SEM, standard error of the mean.

analysis (see Appendix E in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.12.009). The overall conclusion of this study would not change when using any of these different approaches.

Combination Trial

The diagnostic block costs (mean difference €121; 95% CI, 36-187) and minimal interventional treatment costs (mean difference 773; 95% CI, 620-950) were significantly higher in the intervention group than in the control group (Table 2). The total societal costs were lower in the intervention group by –1124 (95% CI, –9111 to 4001). All other between-group differences in total and disaggregate societal costs were not statistically significant (Table 2).

The ICER indicated that radiofrequency denervation combined with a standardized exercise program dominated a standardized exercise program alone (ie, the combination was less costly and more effective; Table 3 and Appendix G in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.12.009). Nevertheless, the uncertainty surrounding the ICER was large. The maximum probability of the intervention being cost-effective compared with the control condition was 0.65 at a ceiling ratio of €30 000 per QALY (Fig. 3).

Table 3. Differences in pooled mean costs and effects (95% confidence interval), incremental cost-effectiveness ratios, and the distribution of incremental cost-effect pairs around the quadrants of the cost-effectiveness planes.

Analysis	Sample size		Outcome	ΔC (95% CI)	ΔE (95% CI)	ICER	Distribution CE-plane (%)			
FACET	Int.	Control		€	Point	€/point	NE	SE	SW	NW
Main analysis – Imputed dataset EQ-5D	125	126	QALY EQ5D (0-1)	1150 (−104 to 2476)	−0.022 (−0.067 to 0.022)	−50 036	14.0	1.9	2.2	81.9
SA1 – SF6D	125	126	QALY SF6D (0-1)	1150 (−104 to 2476)	−0.0008 (−0.014 to 0.012)	−1 531 177	43.6	2.6	1.5	52.4
SA2 – HCA	125	126	QALY EQ5D (0-1)	1185 (−78 to 2472)	−0.023 (−0.067 to 0.022)	−50 035	14.0	1.9	2.2	81.9
SA3 – complete cases	84	88	QALY EQ5D (0-1)	1025 (−314 to 2515)	−0.004 (−0.052 to 0.043)	−274 175	39.1	5.4	1.4	54.1
SA4 – 3 month follow-up	125	126	QALY EQ5D (0-1)	1155 (701 to 1835)	−0.006 (−0.019 to 0.006)	−181 887	17.4	0	0	82.6
Analysis	**Sample size**		**Outcome**	**ΔC (95% CI)**	**ΔE (95% CI)**	**ICER**	**Distribution CE-plane (%)**			
SI	Int.	Control		€	Point	€/point	NE	SE	SW	NW
Main analysis – Imputed dataset	125	126	QALY EQ5D (0-1)	1934 (348-3649)	−0.015 (−0.065 to 0.033)	−120 914	23.9	0.6	0.4	75.0
SA1 – SF6D	125	126	QALY SF6D (0-1)	1934 (348-3649)	−0.016 (−0.037 to 0.006)	−123 694	7.4	0.2	0.9	91.5
SA2 – HCA	125	126	QALY EQ5D (0-1)	1935 (350-3651)	−0.015 (−0.065 to 0.033)	−121 025	23.9	0.6	0.5	75.0
SA3 – complete cases	84	88	QALY EQ5D (0-1)	2417 (711-4344)	−0.019 (−0.073 to 0.028)	−122 910	21.4	0.1	0.1	78.4
SA4 – 3 month follow-up	125	126	QALY EQ5D (0-1)	1661 (859-2956)	−0.002 (−0.017 to 0.013)	−840 092	38.1	0	0	61.9
Analysis	**Sample size**		**Outcome**	**ΔC (95% CI)**	**ΔE (95% CI)**	**ICER**	**Distribution CE-plane (%)**			
COMBINATION	Int.	Control		€	Point	€/point	NE	SE	SW	NW
Main analysis – Imputed dataset	103	99	QALY EQ5D (0-1)	−1124 (−9035 to 3959)	0.011 (−0.055 to 0.078)	−96 813	17.9	44.5	18.7	18.9
SA1 – SF6D	103	99	QALY SF6D (0-1)	−1124 (−9035 to 3959)	−0.007 (−0.027 to 0.011)	150 292	10.3	11.2	52.1	26.5
SA2 – HCA	103	99	QALY EQ5D (0-1)	−881 (−8803 to 4195)	0.012 (−0.056 to 0.078)	−75 906	20.4	42.0	17.3	20.3
SA3 – complete cases	60	46	QALY EQ5D (0-1)	2455 (−62 to 4971)	−0.042 (−0.11 to 0.038)	−58 981	12.6	16.4	31.4	82.7
SA4 – 3 month follow-up	103	99	QALY EQ5D (0-1)	1222 (195-2209)	0.003 (−0.015 to 0.020)	456 448	60.7	0.1	0.0	38.1

Note. Costs are expressed in 2014 euros.
CE-plane indicates cost-effectiveness plane; CI, confidence interval; HCA, human capital approach; ICER, incremental cost-effectiveness ratio; NE, North-East; NW, North-West; SA, sensitivity analysis; SE, South-East; SW, South-West.

The results of the sensitivity analyses (Table 3 and Appendix E in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.12.009) only showed small changes when using the complete cases and when using outcomes until 3 months (see Appendix E in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.12.009). Although slightly different results were found in the various sensitivity analyses, the overall conclusion of the study would not change when using any of these different approaches (Table 3 and Appendix E in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.12.009).

Discussion

The MINT study included 3 large-scale RCTs to evaluate the effectiveness and cost-effectiveness of adding radiofrequency denervation to a standardized exercise program compared with pursuing a standardized exercise program alone for both isolated sources of pain and a combination thereof in a Dutch healthcare setting. In all 3 RCTs, the difference in QALYs was smaller than the minimal clinically important difference of 0.18, as suggested by Coretti et al.[39] This made the study prone to uncertainties, and differences between the intervention and control groups were mainly caused by differences in costs. In the facet joint RCT, the costs were higher in the intervention group; this was mainly due to the costs of the radiofrequency denervation and the difference was not statistically significant. In the SI joint RTC, total costs were significantly higher for the intervention group. In the combination RCT, the costs of the intervention were higher, but the total societal costs were lower in the intervention group; however, this estimate was rather imprecise. The low probabilities of radiofrequency denervation being cost-effective when added to a standardized exercise program at both the Dutch and UK willingness-to-pay thresholds of €10 000 to €80 000 per QALY

Figure 1. Cost-effectiveness acceptability curve indicating the probability of adding radiofrequency denervation to a standardized exercise program being cost-effective in comparison with a standardized exercise program alone for different ceiling ratios (€) for quality-adjusted life-years for patients with facet joint pain.

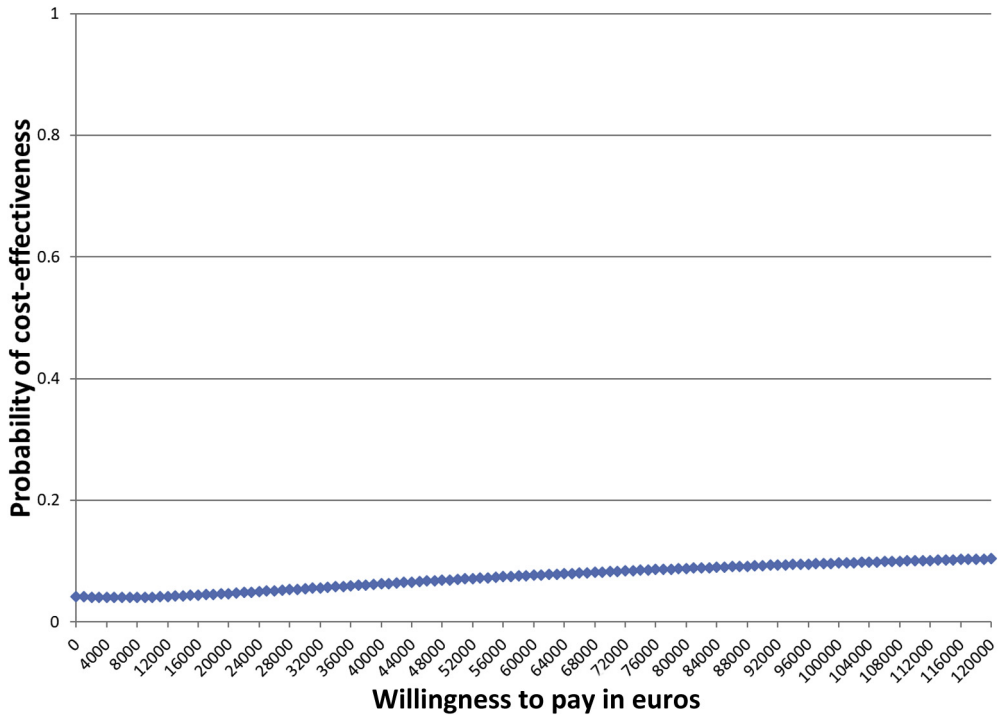


Figure 2. Cost-effectiveness acceptability curve indicating the probability of adding radiofrequency denervation to a standardized exercise program being cost-effective in comparison with a standardized exercise program alone for different ceiling ratios (€) for quality-adjusted life-years for patients with sacroiliac joint pain.

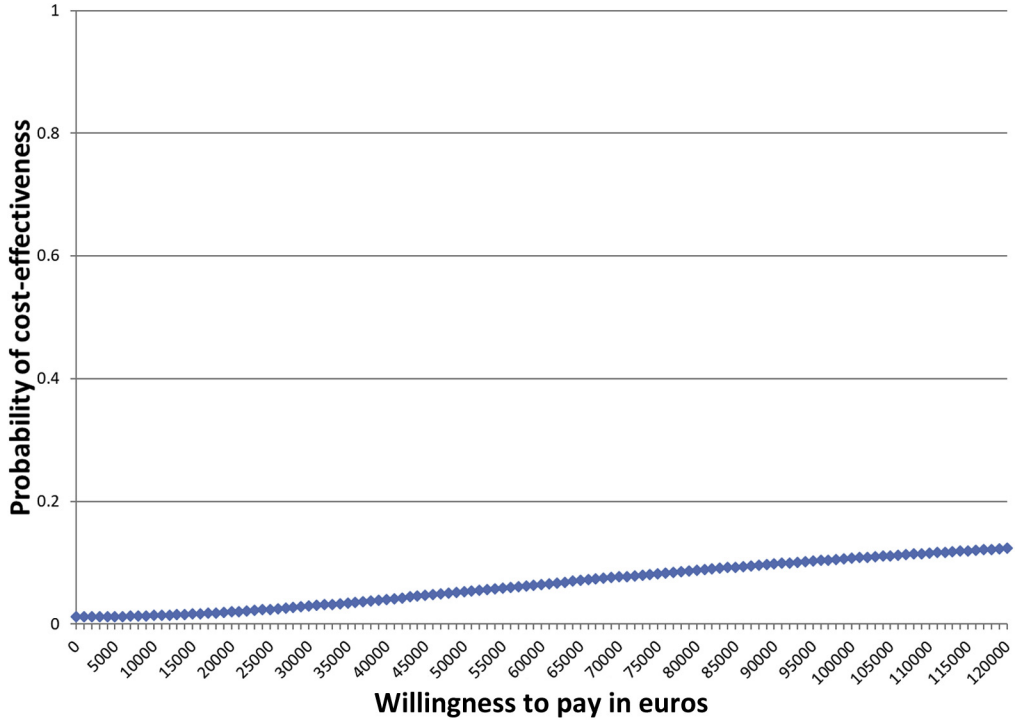
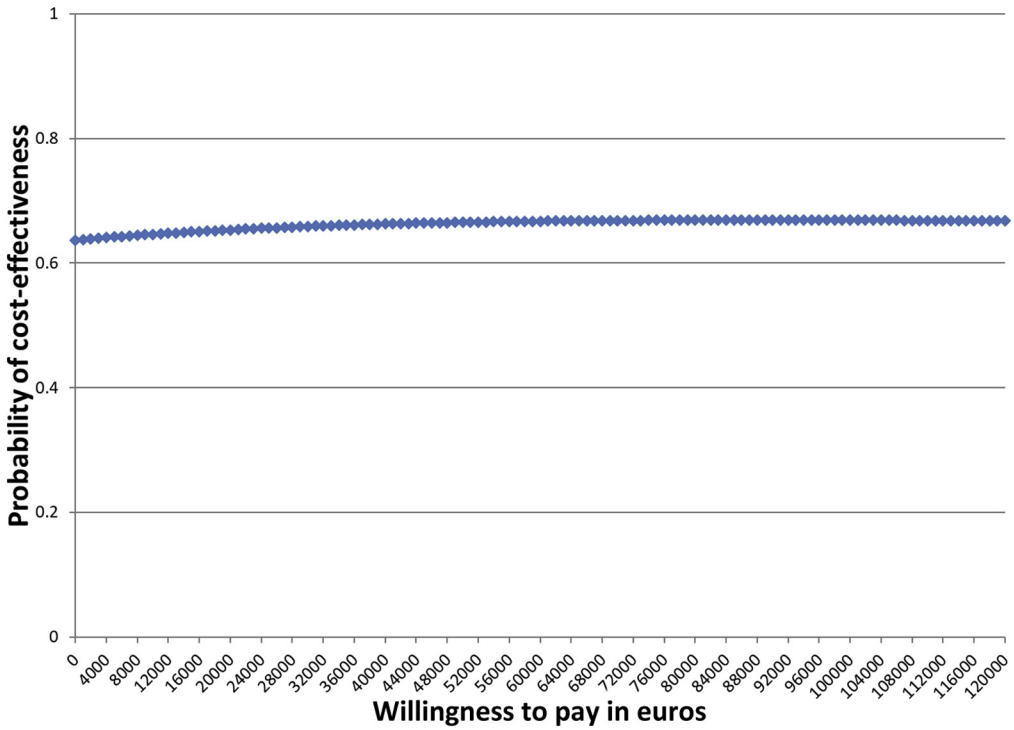


Figure 3. Cost-effectiveness acceptability curve indicating the probability of adding radiofrequency denervation to a standardized exercise program being cost-effective in comparison with a standardized exercise program alone for different ceiling ratios (€) for quality-adjusted life-years for patients with a combination of problems stemming from the facet joints, sacroiliac joints, or intervertebral discs.



and £20 000 per QALY, respectively, suggest that radiofrequency denervation is not cost-effective from a societal perspective in these populations in the Dutch healthcare setting.

When interpreting these results, it should be taken into consideration that economic evaluations are sparse in the field of pain medicine, and evidence regarding the relative cost-effectiveness of radiofrequency denervation versus any alternative strategy is lacking and so future research is warranted.

Interpretation of the Results

Pragmatic study designs are recommended for trial-based economic evaluations.[40] Explanatory trials tend to include highly selected patients, follow strict treatment protocols, and consequently their findings are difficult to extrapolate to real-world clinical practice. Pragmatic trials, such as the MINT study, provide evidence on the relative effectiveness and cost-effectiveness of a treatment in routine clinical practice. Thus the MINT study enabled us to evaluate radiofrequency denervation under real-world circumstances, making the current results generalizable to Dutch clinical practice.[41] Nonetheless, it must be noted that the exercise program, although based on current guidelines and daily practice, was standardized and may vary outside a research setting.

Based on the effectiveness and cost-effectiveness results of the MINT study, the Ministry of Health, Welfare, and Sport in The Netherlands did not change their previous decision to discontinue reimbursement of radiofrequency denervation for patients with chronic low back pain. The results of the facet joint and SI joint pain trials seem rather straightforward, whereas the results of the combination trial are more challenging to interpret. First, the 0.65 probability of radiofrequency denervation being cost-effective when added to exercise therapy at a ceiling ratio of €30 000 per QALY gained is not convincing but is still promising for future research. It also depends on whether decision makers consider a 0.65 probability of cost-effectiveness reasonable at a ceiling ratio of €30 000 per QALY gained. Although the ICER of the combination trial lies in the south-eastern quadrant, the difference in effect is rather small. This suggests that the difference in results between the combination RCT and the other 2 RCTs was mostly caused by a difference in costs (which is −1290; 95% CI, −7852 to 3453). This in turn was likely caused by the difference in study design. Patients in the combination RCT were only randomized after having received a diagnostic block. This resulted in a smaller difference in costs between the control and the intervention group for the combination trial compared with the other 2 trials. Second, patients with pain coming from more than one structure in the back may have more complex symptoms, which can result in more healthcare utilization and absenteeism and could explain the higher costs. Third, complete data could only be collected for 44% of the participants in the combination trial. Missing data are generally inevitable in trial-based economic evaluations, and multiple imputation techniques were used in the main analysis to handle missing data. Multiple imputation is considered the most appropriate method for imputing cost data to avoid loss of power and inefficiency associated with complete-case analyses.[34]

Strengths and Limitations

The pragmatic design of the MINT study is the recommended approach for a trial-based economic evaluation and was proposed to inform policy makers who use the new funding model by the Ministry of Health, Welfare, and Sport and the Netherlands Organization for Health Research and Development. Nevertheless, the MINT study had strengths and limitations that led to extensive discussion among stakeholders.

First, patient selection and interventions were performed as in Dutch daily practice. We were transparent in the description of the procedures and acknowledge possible differences in techniques between countries and settings. Needle size and placement, duration, and temperature of radiofrequency denervation could be some of these differences. Single versus double blocks and thresholds for a positive diagnosis were also a matter of controversy. A single diagnostic block is recommended in the Dutch guidelines.[42] Performing a single block could result in lower specificity and higher false positive rates; however, defining a positive block as pain reduction of 50% or greater, as done in this study, is the most frequently used method in RCTs.[43] Also, scientific studies have not yet identified the best method for selecting patients for radiofrequency denervation. Cohen et al showed no favorable outcome of double blocks over no blocks or single blocks in the facet joint.[44]

A recent Cochrane review also showed that RCTs on radiofrequency denervation are heterogeneous with respect to inclusion criteria, diagnostic methods, and treatment methods.[12] We used a 22-gauge needle, which is standard practice in The Netherlands and based on scientific literature.[45] Researchers and clinicians in other countries or settings should evaluate whether these procedures reflect their daily practice. To illustrate, the National Institute for Health Research reflected on the effectiveness results of the MINT study, concluding that the findings may not be directly applicable in the UK, but certainly raise doubt regarding its use.[46] Performing a comparable RCT with economic evaluation in other countries may identify whether or not our results are generalizable.

Second, the large sample randomized in well-balanced groups reduced the possibility of sampling errors and selection bias.[31] Despite randomization, the intervention groups in all trials had an average of 12 years of low back pain versus 8 years in the control group. We argue that this difference is unlikely to cause any substantial prognostic difference. Furthermore, we adjusted the analysis for duration of pain at baseline, thereby eliminating its potential bias. SUR analyses were used for the cost and effect components of the CUA, allowing us to adjust for various confounders that are not required to be the same for costs and effects.[35]

Third, patients and clinicians could not be blinded, which may have affected the self-reported outcome measures and possibly overestimated the short-term effects. Patients knew their assigned treatment, and 25% to 35% of control participants had radiofrequency denervation after the 3-month restricted study period. This crossover is a limitation that decreased the contrast between the groups and could have affected our results. Nevertheless, the per-protocol analysis as performed in the effectiveness study[17] did not show different results compared with the intention-to-treat approach, which was used for the CUA. Moreover, the sensitivity analysis, which used the 3-month follow-up data before the crossover occurred, also showed similar results to the main CUA at the 12-month follow-up. Therefore, we believe the results are rather robust and not substantially affected by crossover.

Fourth, self-reported retrospective cost questionnaires were used, and presentism costs were not measured. The use of self-reported cost questionnaires may have introduced recall bias. Nevertheless, we tried to limit this by reducing the recall period to 3 months.[26] Self-report can also induce "social desirability"; however, as it seems unlikely that recall bias or the degree to which participants gave socially desirable answers systematically differed between groups, it is not expected that self-report biased the results.

Fifth, SUR analyses and BCA bootstrapping were nested in multiple imputation, but it remains unclear whether this is the optimal strategy for trial-based economic evaluations. Only 1 study so far has explored how to combine bootstrapping and multiple imputation.[38] Their results suggest that single imputation nested in the bootstrap percentile method is preferred, but their strategies did not include BCA bootstrapping and SUR analyses, and within their simulations, missings were only created for costs and not for effects. Therefore further research into this area is warranted.

Conclusions

Although equivocal among patients with symptoms in a combination of facet joints, SI joints, or intervertebral discs, evidence suggests that radiofrequency denervation when added to a standardized exercise program in a Dutch healthcare setting (performed with the Dutch selection and treatment techniques) cannot be considered cost-effective from a societal perspective for patients with chronic mechanical low back pain arising from the facet joints or SI joints compared with a standardized exercise program alone.

Acknowledgments

This study was funded by grant 171202013 from the Netherlands Organization for Health Research and Development, by the Dutch Society for Anesthesiology, and the Dutch health insurance companies. We thank Merel van Raamt, PT, and Robert van Cingel, PhD (Sports Medical Centre Papendal [SMCP]), for their help in developing the exercise program. SMCP received financial support from the research grant for the development of the protocol. We also thank all participants, physiotherapists, and everyone working at the participating pain clinics. The participating pain clinics received reimbursement from the research grant for their extra study-related administrative tasks.

Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2019.12.009.

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